REMARKS

The Applicants thank the Examiner for her examination to date and respectfully request reconsideration of the present application in view of the reasons that follow.

Claims 15-17 and 19-25 are pending to be examined on their merits.

Only the obviousness issue remains to be addressed.

I. Substance of the Interview

The Applicants thank Examiners Welter and Channavajjala for extending the courtesy in conducting an in-person interview with the Applicants' representatives on January 25, 2010. During the interview, the unexpected results, including the supporting evidence thereof, submitted in the July 24, 2009 Rule 132 Declaration were discussed.

II. Claims Rejections – 35 U.S.C. § 103

Claims 15-17, 19-21, 23, and 25 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over WO 01/32158 ("Piper") in view of *Practical Pharm. Prep. Tech.,* January 1999, pp. 203-04 ("Zhuang"), as evidenced by *Remington: The Science and Practice of Pharmacy,* 21st Edition, 2003, pp. 675-676 ("Remington") and RxList: the Internet Drug List (http://www.rxlist.com/actos-drug.htm). Claims 22 and 24 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Piper in view of Zhuang, as evidenced by Remington and RxList and US 6,117,451 ("Kumar"). The Applicants respectfully traverse these rejections.

The Office does not find the Applicants' July 24, 2009 Submission and the Declaration by Mr. Koike persuasive because the Office alleges that (1) the Koike Declaration did not show objective evidence and thus was merely an opinion Declaration; (2) the presently claimed ratio of the median particle size is not important; and (3) one of ordinary skill in the art would have reached the presently claimed invention based on the teachings of Piper. *See* Office Action, pp. 10-11. The Applicants respectfully traverse these assertions and address each separately below.

(A) *The unexpected results are supported by objective evidence*

As discussed during the interview, the unexpected results provided in the July 24, 2009 Koike Declaration were not based on opinion; instead, they are based on objective experimental results. The Applicants submit herewith a second Declaration by Mr. Koike to provide these data to supplement the July 24, 2009 Declaration.

In this Declaration, Mr. Koike clearly demonstrates that the bioequivalence of pioglitazone can only be obtained after the pioglitazone is micronized. The Applicants note that a discussion of micronization and the bioequivalence studies has already been provided in the Submission and the Koike Declaration submitted on July 24, 2009. Table DD1 in the present Declaration demonstrates the discrepancies with respect to the bioequivalence of pioglitazone and metformin when the pioglitazone is not micronized. Specifically, while bioequivalence can be achieved for metformin, bioequivalence cannot be attained for pioglitazone when the pioglitazone is not micronized. Such discrepancies are summarized in Table DD2.

Table DD3 demonstrates that these discrepancies can be eliminated by micronizing the pioglitazone – i.e., reducing the particle size of pioglitazone to the presently claimed 2-10 μm range. As already provided in the Submission and the Declaration submitted on July 24, 2009, such a discrepancy can be attributed to an unexpected *in vivo* drug interaction between the two active ingredients taking place in a human body. **This interaction is not only rare but also unpredictable to one of ordinary skill in the art**. For example, as already demonstrated in the previous Submission and Declaration, while Examples 2, 3, 5, and 6 in the present Specification show equivalence *in vitro* (*see* Experimental Example 3), (*in vivo*) bioequivalence test results show that Examples 2 and 3 (pioglitazone size: 13 μm) are **not** bioequivalent, and only Examples 5 and 6 (pioglitazone size: 2-10 μm) are found to be bioequivalent. *See* Tables DD1 and DD3 in the present Koike Declaration).

Even more surprisingly, **<u>the micronization of the pioglitazone particles did not significantly affect the uniformity of either of the active ingredients</u>**, as further demonstrated in Table DD4 of the present Koike Declaration. This finding is in stark contrast to the Office's suggestion that one of ordinary skill in the art would have micronized pioglitazone for the purpose of increasing uniformity. The Office asserts on p. 5 of the Office Action that "... according to Zhuang et al, a more uniform mixture is obtained by having a small particle size of each ingredient and a **<u>similar</u>** size of each ingredient..." In other words, based on the Office's reasoning, to accomplish the particle size uniformity in view of the teachings of Zhuang, one would strive to have the median size of biguanide and that of glyburide (of Piper) to be as **<u>similar</u>** (i.e., as close to a 1:1 ratio) as possible. This is further evidenced in that Zhuang teaches that similarly sized ingredients make a more uniform mixture. However, such a conclusion by the Office is opposite to the results shown in Table DD4 of the present Koike Declaration.

As described in the Examples of the present Specification, the particle size of metformin of the present invention can be, for example, 29 μm. However, as demonstrated by Mr. Koike in the present Koike Declaration, the uniformity of API is not affected even when the particle size of pioglitazone is reduced to 2-10 μm. In other words, contrary to Zhuang's teachings, the present invention need not bring the median size of pioglitazone and metformin closer to 1:1 ratio to achieve uniformity. Such surprising results could not have been expected by one of ordinary skill in the art. Further, as described below, even if the ratio of the particle size were 1:1, without the presently claimed micronized pioglitazone particles, one would not have reached the present invention.

Thus, the Applicants respectfully submit that the Office's assertion that the unexpected results are based only on opinion is rendered moot in view of the data submitted in the present Koike Declaration.

(B) *The presently claimed ratio of median particle size is important*

The Applicants respectfully submit that the present Koike Declaration also renders moot the Office's assertion that the presently claimed ratio is not important. The Applicants respectfully traverse the Office's position that because the ratio is not shown to affect the unexpected results in the July 24, 2009 Koike Declaration, the ratio is not important. To the contrary, as described in the present Koike Declaration, the ratio of the median size of metformin to that of the pioglitazone was held constant during the experiments merely to illustrate the effect of micronization of the pioglitazone; and this should not be construed as an indication that the ratio is unimportant.

Thus, the Applicants respectfully submit that the Office's assertion that the presently recited ratio is unimportant is rendered moot in view of the data submitted in the present Koike Declaration.

(C) *The presently claimed preparations are unexpected over Piper's teachings*

In contrast to the Office's position, the Applicants respectfully submit that one of ordinary skill in the art would not have reached the presently claimed preparations, comprising a single phase, based on Piper's teachings. The Office's reasoning to arrive at its position is that (1) Piper teaches a combination of glyburide and metformin; (2) Piper mentions generally that "...pioglitazone hydrochloride can be paired with metformin..." (Office Action, p.11); and (3) Piper showed a study with particle size data to achieve comparable bioavailability to Micronase... the particle size values or particle distribution assured reproducibility of glyburide dissolution and bioavailability from metformin hydrochloride-glyburide tablets" (Office Action, p. 5). The Applicants respectfully traverse.

At the outset, the Applicants respectfully traverse the Office's analogy between the terms "bioavailability" (as disclosed in Piper) and "bioequivalence" (as discussed herein).

"Bioavailability" and "bioequivalence" refer to different properties and thus should not be used interchangeably.

"Bioavailability" refers to a measurement of the percentage of a therapeutically active drug that is absorbed from a formulation and reaches into the systemic blood circulation from a defined dosage. In other words, a constant range of particle size would show a constant dissolution rate, and thus a constant (reproducible) bioavailability. By contrast, "bioequivalence" refers to the equivalence (e.g., in pharmacological effect) between an original drug and a later developed drug by administering them at their respective usual dosage and comparing the concentration in blood as a result.

Contrary to the Office's assertions on p. 5 of the Office Action, the glyburide of Piper (Glucovance®) shows neither bioavailability nor bioequivalence. The Applicants submit herewith Exhibit A, which is an NDA document by the Assignee of Piper for the glyburide and metformin hydrochloride embodiments described in Piper. As demonstrated in Exhibit A, in stark contrast to the Office's position, Piper merely discloses that bioavailability is reproduced within a certain range of the particle size. Piper's disclosure does not at all describe that a similar bioavailability of Glucovance® to the single agent can be achieved or that they are bioequivalent.

The Applicants respectfully direct the Office's attention to p. 4 and p. 5 of Exhibit A. Contrary to the Office's assertion, as shown in the section related to bioavailability (p. 4 of Exhibit A), the glyburide of Piper shows a **higher** bioavailability than a single agent of glyburide in Micronase, and does **not** conform to each other. Furthermore, as clearly demonstrated on p. 5 of Exhibit A, without the micronization as presently claimed, bioequivalence of glyburide is **not** established – **this is in stark contrast to the Office's assertion and to the presently claimed preparation**. Such a contrast not only renders moot the Office's incorrect assertion, but it also further demonstrates the surprising results with respect to the bioequivalence of pioglitazone of the presently claimed preparations.

Thus, contrary to the Office's assertion, one of ordinary skill in the art would not have reached the present invention based on Piper's teachings.

Additionally, as explained in the July 24, 2009 Submission, none of the other cited references remedies the deficiencies of Piper. The unexpected results set forth above overcome any possible case of *prima facie* obviousness.

Therefore, at least in view of the foregoing, the Applicants respectfully request that the rejections be withdrawn.

CONCLUSION

The Applicants believe that the present application is now in condition for allowance and thus respectfully request favorable reconsideration of the application.

The Office is invited to contact the undersigned by telephone if a telephone interview would advance the prosecution of the present application.

The Office is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, the Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 12, 2010

By [signature]

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EXHIBIT A

Bristol-Myers Squibb Company

GLUCOVANCE®

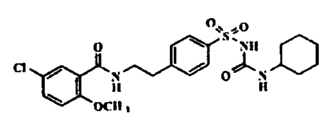
(Glyburide and Metformin HCl Tablets)

1.25 mg/250 mg
2.5 mg/500 mg
5 mg/500 mg

DESCRIPTION

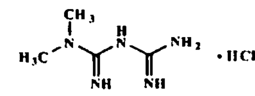
GLUCOVANCE® (Glyburide and Metformin HCl Tablets) contains two oral antihyperglycemic drugs used in the management of type 2 diabetes, glyburide and metformin hydrochloride.

Glyburide is an oral antihyperglycemic drug of the sulfonylurea class. The chemical name for glyburide is 1-[[*p*-[2-(5-chloro-*o*-anisamido)ethyl]phenyl]sulfonyl]-3-cyclo-hexylurea. Glyburide is a white to off-white crystalline compound with a molecular formula of $C_{23}H_{28}ClN_3O_5S$ and a molecular weight of 494.01. The glyburide used in GLUCOVANCE has a particle size distribution of 25% undersize value not more than 6 µm, 50% undersize value not more than 7-10 µm, and 75% undersize value not more than 21 µm. The structural formula is represented below.



Glyburide

Metformin hydrochloride is an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (*N,N*-dimethylimidodicarbonimidic diamide monohydrochloride) is not chemically or pharmacologically related to sulfonylureas, thiazolidinediones, or α-glucosidase inhibitors. It is a white to off-white crystalline compound with a molecular formula of $C_4H_{12}ClN_5$ (monohydrochloride) and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68. The structural formula is as shown:



Metformin Hydrochloride

GLUCOVANCE is available for oral administration in tablets containing 1.25 mg glyburide with 250 mg metformin hydrochloride, 2.5 mg glyburide with 500 mg metformin hydrochloride, and 5 mg glyburide with 500 mg metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate. The tablets are film coated, which provides color differentiation.

CLINICAL PHARMACOLOGY

Mechanism of Action

GLUCOVANCE combines glyburide and metformin hydrochloride, two antihyperglycemic agents with complementary mechanisms of action, to improve glycemic control in patients with type 2 diabetes.

Glyburide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in patients with type 2 diabetes, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

Metformin hydrochloride is an antihyperglycemic agent that improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.

Pharmacokinetics

Absorption and Bioavailability

GLUCOVANCE

In bioavailability studies of GLUCOVANCE 2.5 mg/500 mg and 5 mg/500 mg, the mean area under the plasma concentration versus time curve (AUC) for the glyburide component was 18% and 7%, respectively, greater than that of the Micronase® brand of glyburide coadministered with metformin. The glyburide component of GLUCOVANCE, therefore, is not bioequivalent to Micronase®.

The metformin component of GLUCOVANCE is bioequivalent to metformin coadministered with glyburide.

Following administration of a single GLUCOVANCE 5 mg/500 mg tablet with either a 20% glucose solution or a 20% glucose solution with food, there was no effect of food on the C_{max} and a relatively small effect of food on the AUC of the glyburide component. The T_{max} for the glyburide component was shortened from 7.5 hours to 2.75 hours with food compared to the same tablet strength administered fasting with a 20% glucose solution. The clinical significance of an earlier T_{max} for glyburide after food is not known. The effect of food on the pharmacokinetics of the metformin component was indeterminate.

Glyburide

Single-dose studies with Micronase® tablets in normal subjects demonstrate significant absorption of glyburide within one hour, peak drug levels at about four hours, and low but detectable levels at twenty-four hours. Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Bioequivalence has not been established between GLUCOVANCE and single ingredient glyburide products.

Metformin Hydrochloride

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximately 50 to 60%. Studies using single oral doses of metformin tablets of 500 mg and 1500 mg, and 850 mg to 2550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin, as shown by approximately a 40% lower peak concentration and a 25% lower AUC in plasma and a 35-minute prolongation of time to peak plasma concentration following administration of a single 850 mg tablet of metformin with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Glyburide

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic.

Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding glyburide. It has not been shown that this difference in protein binding results in fewer drug-drug interactions with glyburide tablets in clinical use.

Metformin Hydrochloride

The apparent volume of distribution (V/F) of metformin following single oral doses of 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin, steady state plasma concentrations of metformin are reached within 24 to 48 hours and are generally <1 μg/mL. During controlled clinical trials, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

Metabolism and Elimination

Glyburide

The decrease of glyburide in the serum of normal healthy individuals is biphasic; the terminal half-life is about 10 hours. The major metabolite of glyburide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active ($1/400^{th}$ and 1/40th as active, respectively, as glyburide) in rabbits. Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Metformin Hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion. Renal clearance (see **Table 1**) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Patients With Type 2 Diabetes

Multiple-dose studies with glyburide in patients with type 2 diabetes demonstrate drug level concentration-time curves similar to single-dose studies, indicating no buildup of drug in tissue depots.

In the presence of normal renal function, there are no differences between single- or multiple-dose pharmacokinetics of metformin between patients with type 2 diabetes and normal subjects (see **Table 1**), nor is there any accumulation of metformin in either group at usual clinical doses.

Hepatic Insufficiency

No pharmacokinetic studies have been conducted in patients with hepatic insufficiency for either glyburide or metformin.

Renal Insufficiency

No information is available on the pharmacokinetics of glyburide in patients with renal insufficiency.

In patients with decreased renal function (based on creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (see **Table 1**; also, see **WARNINGS**).

Geriatrics

There is no information on the pharmacokinetics of glyburide in elderly patients.

Limited data from controlled pharmacokinetic studies of metformin in healthy elderly subjects suggest that total plasma clearance is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (see **Table 1**). Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Table 1: Select Mean (±S.D.) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Metformin

Subject Groups: Metformin Dose[a] (number of subjects)	C_{max}[b] (μg/mL)	T_{max}[c] (hrs)	Renal Clearance (mL/min)
Healthy, nondiabetic adults:			
500 mg SD[d] (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg SD (74)[e]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg t.i.d. for 19 doses[f] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes:			
850 mg SD (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg t.i.d. for 19 doses[f] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[g], healthy nondiabetic adults:			
850 mg SD (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults: 850 mg SD			
Mild (CL_{cr}[h] 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a] All doses given fasting except the first 18 doses of the multiple-dose studies
[b] Peak plasma concentration
[c] Time to peak plasma concentration
[d] SD=single dose
[e] Combined results (average means) of five studies: mean age 32 years (range 23-59 years)
[f] Kinetic study done following dose 19, given fasting
[g] Elderly subjects, mean age 71 years (range 65-81 years)
[h] CL_{cr}=creatinine clearance normalized to body surface area of 1.73 m^2

Pediatrics

After administration of a single oral GLUCOPHAGE® (metformin hydrochloride) 500 mg tablet with food, geometric mean metformin C_{max} and AUC differed less than 5% between pediatric type 2 diabetic patients (12 to 16 years of age) and gender- and weight-matched healthy adults (20 to 45 years of age), all with normal renal function.

After administration of a single oral GLUCOVANCE tablet with food, dose-normalized geometric mean glyburide C_{max} and AUC in pediatric patients with type 2 diabetes (11 to 16 years of age, n=28, mean body weight of 97 kg) differed less than 6% from historical values in healthy adults.

Gender

There is no information on the effect of gender on the pharmacokinetics of glyburide.

Metformin pharmacokinetic parameters did not differ significantly in subjects with or without type 2 diabetes when analyzed according to gender (males=19, females=16). Similarly, in controlled clinical studies in patients with type 2 diabetes, the antihyperglycemic effect of metformin was comparable in males and females.

Race

No information is available on race differences in the pharmacokinetics of glyburide.

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Clinical Studies

Patients with Inadequate Glycemic Control on Diet and Exercise Alone

In a 20-week, double-blind, multicenter U.S. clinical trial, a total of 806 drug-naive patients with type 2 diabetes, whose hyperglycemia was not adequately controlled with diet and exercise alone (baseline fasting plasma glucose [FPG] <240 mg/dL, baseline hemoglobin A_{1c} [HbA_{1c}] between 7% and 11%), were randomized to receive initial therapy with placebo, 2.5 mg glyburide, 500 mg metformin, GLUCOVANCE 1.25 mg/250 mg, or GLUCOVANCE 2.5 mg/500 mg. After four weeks, the dose was progressively increased (up to the eight-week visit) to a maximum of four tablets daily as needed to reach a target FPG of 126 mg/dL. Trial data at 20 weeks are summarized in **Table 2**.

Table 2: Placebo- and Active-Controlled Trial of GLUCOVANCE in Patients with Inadequate Glycemic Control on Diet and Exercise Alone: Summary of Trial Data at 20 Weeks

	Placebo	Glyburide 2.5 mg tablets	Metformin 500 mg tablets	GLUCOVANCE 1.25 mg/250 mg tablets	GLUCOVANCE 2.5 mg/500 mg tablets
Mean Final Dose	0 mg	5.3 mg	1317 mg	2.78 mg/557 mg	4.1 mg/824 mg
Hemoglobin A_{1c}	N=147	N=142	N=141	N=149	N=152
Baseline Mean (%)	8.14	8.14	8.23	8.22	8.20
Mean Change from Baseline	-0.21	-1.24	-1.03	-1.48	-1.53
Difference from Placebo		-1.02	-0.82	-1.26^{a}	-1.31^{a}
Difference from Glyburide				-0.24^{b}	-0.29^{b}
Difference from Metformin				-0.44^{b}	-0.49^{b}
Fasting Plasma Glucose	N=159	N=158	N=156	N=153	N=154
Baseline Mean FPG (mg/dL)	177.2	178.9	175.1	178	176.6
Mean Change from Baseline	4.6	-35.7	-21.2	-41.5	-40.1
Difference from Placebo		-40.3	-25.8	-46.1^{a}	-44.7^{a}
Difference from Glyburide				-5.8^{c}	-4.5^{c}
Difference from Metformin				-20.3^{c}	-18.9^{c}
Body Weight Mean Change from Baseline	-0.7 kg	+1.7 kg	-0.6 kg	+1.4 kg	+1.9 kg
Final HbA_{1c} Distribution (%)	N=147	N=142	N=141	N=149	N=152
<7%	19.7%	59.9%	50.4%	66.4%	71.7%
≥7% and <8%	37.4%	26.1%	29.8%	25.5%	19.1%
≥8%	42.9%	14.1%	19.9%	8.1%	9.2%

[a] p<0.001
[b] p<0.05
[c] p=NS

Treatment with GLUCOVANCE resulted in significantly greater reduction in HbA_{1c} and postprandial plasma glucose (PPG) compared to glyburide, metformin, or placebo. Also, GLUCOVANCE therapy resulted in greater reduction in FPG compared to glyburide, metformin, or placebo, but the differences from glyburide and metformin did not reach statistical significance.

Changes in the lipid profile associated with GLUCOVANCE treatment were similar to those seen with glyburide, metformin, and placebo.

The double-blind, placebo-controlled trial described above restricted enrollment to patients with HbA_{1c} <11% or FPG <240 mg/dL. Screened patients ineligible for the first trial because of HbA_{1c} and/or FPG exceeding these limits were treated directly with GLUCOVANCE 2.5 mg/500 mg in an open-label, uncontrolled protocol. In this study, three out of 173 patients (1.7%) discontinued because of inadequate therapeutic response. Across the group of 144 patients who completed 26 weeks of treatment, mean HbA_{1c} was reduced from a baseline of 10.6% to 7.1%. The mean baseline FPG was 283 mg/dL and was reduced to 164 and 161 mg/dL after 2 and 26 weeks, respectively. The mean final titrated dose of GLUCOVANCE was 7.85 mg/1569 mg (equivalent to approximately three GLUCOVANCE 2.5 mg/500 mg tablets per day).

Patients with Inadequate Glycemic Control on Sulfonylurea Alone

In a 16-week, double-blind, active-controlled U.S. clinical trial, a total of 639 patients with type 2 diabetes not adequately controlled (mean baseline HbA_{1c} 9.5%, mean baseline FPG 213 mg/dL) while being treated with at least one-half the maximum dose of a sulfonylurea (e.g., glyburide 10 mg, glipizide 20 mg) were randomized to receive glyburide (fixed dose, 20 mg), metformin (500 mg), GLUCOVANCE 2.5 mg/500 mg, or GLUCOVANCE 5 mg/500 mg. The doses of metformin and GLUCOVANCE were titrated to a maximum of four tablets daily as needed to achieve FPG <140 mg/dL. Trial data at 16 weeks are summarized in **Table 3**.

Table 3: GLUCOVANCE in Patients with Inadequate Glycemic Control on Sulfonylurea Alone: Summary of Trial Data at 16 Weeks

	Glyburide 5 mg tablets	Metformin 500 mg tablets	GLUCOVANCE 2.5 mg/500 mg tablets	GLUCOVANCE 5 mg/500 mg tablets
Mean Final Dose	20 mg	1840 mg	8.8 mg/1760 mg	17 mg/1740 mg
Hemoglobin A_{1c}	N=158	N=142	N=154	N=159
Baseline Mean (%)	9.63	9.51	9.43	9.44
Final Mean	9.61	9.82	7.92	7.91
Difference from Glyburide			-1.69[a]	-1.70[a]
Difference from Metformin			-1.90[a]	-1.91[a]
Fasting Plasma Glucose	N=163	N=152	N=160	N=160
Baseline Mean (mg/dL)	218.4	213.4	212.2	210.2
Final Mean	221.0	233.8	169.6	161.1
Difference from Glyburide			-51.3[a]	-59.9[a]
Difference from Metformin			-64.2[a]	-72.7[a]
Body Weight Mean Change from Baseline	+0.43 kg	-2.76 kg	+0.75 kg	+0.47 kg
Final HbA_{1c} Distribution (%)	N=158	N=142	N=154	N=159
<7%	2.5%	2.8%	24.7%	22.6%
≥7% and <8%	9.5%	11.3%	33.1%	37.1%
≥8%	88%	85.9%	42.2%	40.3%

[a] $p<0.001$

After 16 weeks, there was no significant change in the mean HbA_{1c} in patients randomized to glyburide or to metformin therapy. Treatment with GLUCOVANCE at doses up to 20 mg/2000 mg per day resulted in significant lowering of HbA_{1c}, FPG, and PPG from baseline compared to glyburide or metformin alone.

Addition of Thiazolidinediones to GLUCOVANCE Therapy

In a 24-week, double-blind, multicenter U.S. clinical trial, patients with type 2 diabetes not adequately controlled on current oral antihyperglycemic therapy (either monotherapy or combination therapy) were first switched to open label GLUCOVANCE 2.5 mg/500 mg tablets and titrated to a maximum daily dose of 10 mg/2000 mg. A total of 365 patients inadequately controlled (HbA_{1c} >7.0% and ≤10%) after 10 to 12 weeks of a daily GLUCOVANCE dose of at least 7.5 mg/1500 mg were randomized to receive add-on therapy with rosiglitazone 4 mg or placebo once daily. After eight weeks, the rosiglitazone dose was increased to a maximum of 8 mg daily as needed to reach a target mean daily glucose of 126 mg/dL or HbA_{1c} <7%. Trial data at 24 weeks or at the last prior visit are summarized in **Table 4**.

Table 4:	**Effects of Adding Rosiglitazone or Placebo in Patients Treated with GLUCOVANCE in a 24-Week Trial**	
	Placebo + GLUCOVANCE	**Rosiglitazone + GLUCOVANCE**
Mean Final Dose GLUCOVANCE Rosiglitazone	10 mg/1992 mg 0 mg	9.6 mg/1914 mg 7.4 mg
Hemoglobin A_{1c}	N=178	N=177
Baseline Mean (%)	8.09	8.14
Final Mean	8.21	7.23
Difference from Placebo[a]		-1.02[b]
Fasting Plasma Glucose	N=181	N=176
Baseline Mean (mg/dL)	173.1	178.4
Final Mean	181.4	136.3
Difference from Placebo[a]		-48.5[b]
Body Weight Mean Change from Baseline	+0.03 kg	+3.03 kg
Final HbA_{1c} Distribution (%)	N=178	N=177
<7%	13.5%	42.4%
≥7% and <8%	32.0%	38.4%
≥8%	54.5%	19.2%

[a] Adjusted for the baseline mean difference
[b] $p<0.001$

For patients who did not achieve adequate glycemic control on GLUCOVANCE, the addition of rosiglitazone, compared to placebo, resulted in significant lowering of HbA_{1c} and FPG.

INDICATIONS AND USAGE

GLUCOVANCE is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

GLUCOVANCE (Glyburide and Metformin HCl Tablets) is contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females], or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS** and **PRECAUTIONS**).

2. Known hypersensitivity to metformin hydrochloride or glyburide.

3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

GLUCOVANCE should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function. (See also **PRECAUTIONS.**)

WARNINGS

Metformin Hydrochloride

Lactic acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with GLUCOVANCE; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). In more than 20,000 patient-years exposure to metformin in clinical trials, there were no reports of lactic acidosis. Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. GLUCOVANCE treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, GLUCOVANCE should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, GLUCOVANCE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking GLUCOVANCE, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, GLUCOVANCE should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). GLUCOVANCE should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of GLUCOVANCE, gastrointestinal symptoms, which are common during initiation of therapy with metformin, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking GLUCOVANCE do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling. (See also PRECAUTIONS.)

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking GLUCOVANCE, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery. (See also CONTRAINDICATIONS and PRECAUTIONS.)

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs in preventing or delaying vascular complications in patients with non-insulin-dependent diabetes. The study involved 823 patients who were randomly assigned to one of four treatment groups (*Diabetes* 19 (Suppl. 2):747-830, 1970).

UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 g per day) had a rate of cardiovascular mortality approximately 2-1/2 times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality.

Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and benefits of glyburide and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

General

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLUCOVANCE or any other anti-diabetic drug.

GLUCOVANCE

Hypoglycemia

GLUCOVANCE is capable of producing hypoglycemia or hypoglycemic symptoms, therefore, proper patient selection, dosing, and instructions are important to avoid potential hypoglycemic episodes. The risk of hypoglycemia is increased when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents or ethanol. Renal or hepatic insufficiency may cause elevated drug levels of both glyburide and metformin hydrochloride and the hepatic insufficiency may also diminish gluconeogenic capacity, both of which increase the risk of hypoglycemic reactions. Elderly, debilitated, or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Metformin Hydrochloride

Monitoring of renal function

Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive GLUCOVANCE. In patients with advanced age, GLUCOVANCE should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function.

In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, GLUCOVANCE should not be titrated to the maximum dose (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**). Before initiation of GLUCOVANCE therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and GLUCOVANCE discontinued if evidence of renal impairment is present.

Use of concomitant medications that may affect renal function or metformin disposition

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **PRECAUTIONS**: **Drug Interactions**), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials)

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, GLUCOVANCE should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal.

Hypoxic states

Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction, and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on GLUCOVANCE therapy, the drug should be promptly discontinued.

Surgical procedures

GLUCOVANCE therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism.

Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving GLUCOVANCE. Due to its effect on the gluconeogenic capacity of the liver, alcohol may also increase the risk of hypoglycemia.

Impaired hepatic function

Since impaired hepatic function has been associated with some cases of lactic acidosis, GLUCOVANCE should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels

In controlled clinical trials with metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum vitamin B_{12}, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on metformin and any apparent abnormalities should be appropriately investigated and managed (see **PRECAUTIONS**: **Laboratory Tests**).

Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes

A patient with type 2 diabetes previously well controlled on metformin who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, GLUCOVANCE must be stopped immediately and other appropriate corrective measures initiated (see also **WARNINGS**).

Addition of Thiazolidinediones to GLUCOVANCE Therapy

Hypoglycemia

Patients receiving GLUCOVANCE in combination with a thiazolidinedione may be at risk for hypoglycemia.

Weight gain

Weight gain was seen with the addition of rosiglitazone to GLUCOVANCE, similar to that reported for thiazolidinedione therapy alone.

Hepatic effects

When a thiazolidinedione is used in combination with GLUCOVANCE, periodic monitoring of liver function tests should be performed in compliance with the labeled recommendations for the thiazolidinedione.

Information for Patients

GLUCOVANCE

Patients should be informed of the potential risks and benefits of GLUCOVANCE and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis associated with metformin therapy, its symptoms, and conditions that predispose to its development, as noted in the **WARNINGS** and **PRECAUTIONS** sections, should be explained to patients. Patients should be advised to discontinue GLUCOVANCE immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of GLUCOVANCE, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

The risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving GLUCOVANCE. (See **Patient Information** printed below.)

Laboratory Tests

Periodic fasting blood glucose and glycosylated hemoglobin (HbA_{1c}) measurements should be performed to monitor therapeutic response.

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with metformin therapy, if this is suspected, vitamin B_{12} deficiency should be excluded.

Drug Interactions

GLUCOVANCE

Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving GLUCOVANCE, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving GLUCOVANCE, the patient should be observed closely for hypoglycemia. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid as compared to sulfonylureas, which are extensively bound to serum proteins.

Glyburide

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving GLUCOVANCE, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving GLUCOVANCE, the patient should be observed closely for loss of blood glucose control.

A possible interaction between glyburide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of glyburide. The mechanism for this interaction is not known.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical, or vaginal preparations of miconazole is not known.

Metformin Hydrochloride

Furosemide

A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by coadministration.

Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when coadministered chronically.

Nifedipine

A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that coadministration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs

Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of GLUCOVANCE and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other

In healthy volunteers, the pharmacokinetics of metformin and propranolol and metformin and ibuprofen were not affected when coadministered in single-dose interaction studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been conducted with the combined products in GLUCOVANCE. The following data are based on findings in studies performed with the individual products.

Glyburide

Studies in rats with glyburide alone at doses up to 300 mg/kg/day (approximately 145 times the maximum recommended human daily dose of 20 mg for the glyburide component of GLUCOVANCE based on body surface area comparisons) for 18 months revealed no carcinogenic effects. In a two-year oncogenicity study of glyburide in mice, there was no evidence of treatment-related tumors.

There was no evidence of mutagenic potential of glyburide alone in the following *in vitro* tests: *Salmonella* microsome test (Ames test) and in the DNA damage/alkaline elution assay.

Metformin Hydrochloride

Long-term carcinogenicity studies were performed with metformin alone in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg of the metformin component of GLUCOVANCE based on body surface area comparisons. No evidence of carcinogenicity with metformin alone was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin alone in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day of metformin alone.

There was no evidence of a mutagenic potential of metformin alone in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin alone when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose of the metformin component of GLUCOVANCE based on body surface area comparisons.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible. Because animal reproduction studies are not always predictive of human response, GLUCOVANCE should not be used during pregnancy unless clearly needed. (See below.)

There are no adequate and well-controlled studies in pregnant women with GLUCOVANCE or its individual components. No animal studies have been conducted with the combined products in GLUCOVANCE. The following data are based on findings in studies performed with the individual products.

Glyburide

Reproduction studies were performed in rats and rabbits at doses up to 500 times the maximum recommended human daily dose of 20 mg of the glyburide component of GLUCOVANCE based on body surface area comparisons and revealed no evidence of impaired fertility or harm to the fetus due to glyburide.

Metformin Hydrochloride

Metformin alone was not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg of the metformin component of GLUCOVANCE based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nonteratogenic Effects

Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. It is not recommended that GLUCOVANCE be used during pregnancy. However, if it is used, GLUCOVANCE should be discontinued at least two weeks before the expected delivery date. (See **Pregnancy**: **Teratogenic Effects**: **Pregnancy Category B.**)

Nursing Mothers

Although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue GLUCOVANCE, taking into account the importance of the drug to the mother. If GLUCOVANCE is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

The safety and efficacy of GLUCOVANCE were evaluated in an active-controlled, double-blind, 26-week randomized trial involving a total of 167 pediatric patients (ranging from 9 to 16 years of age) with type 2 diabetes. GLUCOVANCE was not shown statistically to be superior to either metformin or glyburide with respect to reducing HbA_{1c} from baseline (see **Table 5**). No unexpected safety findings were associated with GLUCOVANCE in this trial.

Table 5: HbA_{1c} (Percent) Change From Baseline at 26 Weeks: Pediatric Study

	Glyburide 2.5 mg tablets	Metformin 500 mg tablets	GLUCOVANCE 1.25 mg/250 mg tablets
Mean Final Dose	6.5 mg	1500 mg	3.1 mg/623 mg
Hemoglobin A_{1c}	N=49	N=54	N=57
Baseline Mean (%)	7.70	7.99	7.85
Mean Change from Baseline	-0.96	-0.48	-0.80
Difference from Metformin			-0.32
Difference from Glyburide			+0.16

Geriatric Use

Of the 642 patients who received GLUCOVANCE in double-blind clinical studies, 23.8% were 65 and older while 2.8% were 75 and older. Of the 1302 patients who received GLUCOVANCE in open-label clinical studies, 20.7% were 65 and older while 2.5% were 75 and older. No overall differences in effectiveness or safety were observed between these patients and younger patients, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Metformin hydrochloride is known to be substantially excreted by the kidney and because the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, GLUCOVANCE should only be used in patients with normal renal function (see **CONTRAINDICATIONS**, **WARNINGS**, and **CLINICAL PHARMACOLOGY: Pharmacokinetics**). Because aging is associated with reduced renal function, GLUCOVANCE should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of GLUCOVANCE (see also **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

GLUCOVANCE

In double-blind clinical trials involving GLUCOVANCE as initial therapy or as second-line therapy, a total of 642 patients received GLUCOVANCE, 312 received metformin therapy, 324 received glyburide therapy, and 161 received placebo. The percent of patients reporting events and types of adverse events reported in clinical trials of GLUCOVANCE (all strengths) as initial therapy and second-line therapy are listed in **Table 6**.

Table 6: Most Common Clinical Adverse Events (>5 Percent) in Double-Blind Clinical Studies of GLUCOVANCE Used as Initial or Second-Line Therapy

Adverse Event	Number (%) of Patients			
	Placebo N=161	Glyburide N=324	Metformin N=312	GLUCOVANCE N=642
Upper respiratory infection	22 (13.7)	57 (17.6)	51 (16.3)	111 (17.3)
Diarrhea	9 (5.6)	20 (6.2)	64 (20.5)	109 (17.0)
Headache	17 (10.6)	37 (11.4)	29 (9.3)	57 (8.9)
Nausea/vomiting	10 (6.2)	17 (5.2)	38 (12.2)	49 (7.6)
Abdominal pain	6 (3.7)	10 (3.1)	25 (8.0)	44 (6.9)
Dizziness	7 (4.3)	18 (5.6)	12 (3.8)	35 (5.5)

In a controlled clinical trial of rosiglitazone versus placebo in patients treated with GLUCOVANCE (n=365), 181 patients received GLUCOVANCE with rosiglitazone and 184 received GLUCOVANCE with placebo.

Edema was reported in 7.7% (14/181) of patients treated with rosiglitazone compared to 2.2% (4/184) of patients treated with placebo. A mean weight gain of 3 kg was observed in rosiglitazone-treated patients.

Disulfiram-like reactions have very rarely been reported in patients treated with glyburide tablets.

Hypoglycemia

In controlled clinical trials of GLUCOVANCE there were no hypoglycemic episodes requiring medical intervention and/or pharmacologic therapy; all events were managed by the patients. The incidence of reported symptoms of hypoglycemia (such as dizziness, shakiness, sweating, and hunger), in the initial therapy trial of GLUCOVANCE are summarized in **Table 7**. The frequency of hypoglycemic symptoms in patients treated with GLUCOVANCE 1.25 mg/250 mg was highest in patients with a baseline HbA_{1c} <7%, lower in those with a baseline HbA_{1c} of between 7% and 8%, and was comparable to placebo and metformin in those with a baseline HbA_{1c} >8%. For patients with a baseline HbA_{1c} between 8% and 11% treated with GLUCOVANCE 2.5 mg/500 mg as initial therapy, the frequency of hypoglycemic symptoms was 30 to 35%. As second-line therapy in patients inadequately controlled on sulfonylurea alone, approximately 6.8% of all patients treated with GLUCOVANCE experienced hypoglycemic symptoms. When rosiglitazone was added to GLUCOVANCE therapy, 22% of patients reported one or more fingerstick glucose measurements ≤50 mg/dL compared to 3.3% of placebo-treated patients. All hypoglycemic events were managed by the patients and only one patient discontinued for hypoglycemia. (See **PRECAUTIONS**: **General: Addition of Thiazolidinediones to GLUCOVANCE Therapy**.)

Gastrointestinal Reactions

The incidence of GI side effects (diarrhea, nausea/vomiting, and abdominal pain) in the initial therapy trial are summarized in **Table 7**. Across all GLUCOVANCE trials, GI symptoms were the most common adverse events with GLUCOVANCE and were more frequent at higher dose levels. In controlled trials, <2% of patients discontinued GLUCOVANCE therapy due to GI adverse events.

Table 7: Treatment Emergent Symptoms of Hypoglycemia or Gastrointestinal Adverse Events in a Placebo- and Active-Controlled Trial of GLUCOVANCE as Initial Therapy

Variable	Placebo N=161	Glyburide Tablets N=160	Metformin Tablets N=159	GLUCOVANCE 1.25 mg/250 mg Tablets N=158	GLUCOVANCE 2.5 mg/500 mg Tablets N=162
Mean Final Dose	0 mg	5.3 mg	1317 mg	2.78 mg/557 mg	4.1 mg/824 mg
Number (%) of patients with symptoms of hypoglycemia	5 (3.1)	34 (21.3)	5 (3.1)	18 (11.4)	61 (37.7)
Number (%) of patients with gastrointestinal adverse events	39 (24.2)	38 (23.8)	69 (43.3)	50 (31.6)	62 (38.3)

OVERDOSAGE

Glyburide

Overdosage of sulfonylureas, including glyburide tablets, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or suspected, the patient should be given a rapid intravenous injection of concentrated (50%) glucose solution. This should be followed by a continuous infusion of a more dilute (10%) glucose solution at a rate that will maintain the blood glucose at a level above 100 mg/dL. Patients should be closely monitored for a minimum of 24 to 48 hours, since hypoglycemia may recur after apparent clinical recovery.

Metformin Hydrochloride

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases (see **WARNINGS**). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

DOSAGE AND ADMINISTRATION

General Considerations

Dosage of GLUCOVANCE must be individualized on the basis of both effectiveness and tolerance while not exceeding the maximum recommended daily dose of 20 mg glyburide/2000 mg metformin. GLUCOVANCE should be given with meals and should be initiated at a low dose, with gradual dose escalation as described below, in order to avoid hypoglycemia (largely due to glyburide), to reduce GI side effects (largely due to metformin), and to permit determination of the minimum effective dose for adequate control of blood glucose for the individual patient.

With initial treatment and during dose titration, appropriate blood glucose monitoring should be used to determine the therapeutic response to GLUCOVANCE and to identify the minimum effective dose for the patient. Thereafter, HbA_{1c} should be measured at intervals of approximately 3 months to assess the effectiveness of therapy. The therapeutic goal in all patients with type 2 diabetes is to decrease FPG, PPG, and HbA_{1c} to normal or as near normal as possible. Ideally, the response to therapy should be evaluated using HbA_{1c} (glycosylated hemoglobin), which is a better indicator of long-term glycemic control than FPG alone.

No studies have been performed specifically examining the safety and efficacy of switching to GLUCOVANCE therapy in patients taking concomitant glyburide (or other sulfonylurea) plus metformin. Changes in glycemic control may occur in such patients, with either hyperglycemia or hypoglycemia possible. Any change in therapy of type 2 diabetes should be undertaken with care and appropriate monitoring.

GLUCOVANCE in Patients with Inadequate Glycemic Control on Diet and Exercise

Recommended starting dose: 1.25 mg/250 mg once or twice daily with meals.

For patients with type 2 diabetes whose hyperglycemia cannot be satisfactorily managed with diet and exercise alone, the recommended starting dose of GLUCOVANCE is 1.25 mg/250 mg once a day with a meal. As initial therapy in patients with baseline HbA_{1c} >9% or an FPG >200 mg/dL, a starting dose of GLUCOVANCE 1.25 mg/250 mg twice daily with the morning and evening meals may be used. Dosage increases should be made in increments of 1.25 mg/250 mg per day every two weeks up to the minimum effective dose necessary to achieve adequate control of blood glucose. In clinical trials of GLUCOVANCE as initial therapy, there was no experience with total daily doses greater than 10 mg/2000 mg per day. **GLUCOVANCE 5 mg/500 mg should not be used as initial therapy due to an increased risk of hypoglycemia.**

GLUCOVANCE Use in Patients with Inadequate Glycemic Control on a Sulfonylurea and/or Metformin

Recommended starting dose: 2.5 mg/500 mg or 5 mg/500 mg twice daily with meals.

For patients not adequately controlled on either glyburide (or another sulfonylurea) or metformin alone, the recommended starting dose of GLUCOVANCE is 2.5 mg/500 mg or 5 mg/500 mg twice daily with the morning and evening meals. In order to avoid hypoglycemia, the starting dose of GLUCOVANCE should not exceed the daily doses of glyburide or metformin already being taken. The daily dose should be titrated in increments of no more than 5 mg/500 mg up to the minimum effective dose to achieve adequate control of blood glucose or to a maximum dose of 20 mg/2000 mg per day.

For patients previously treated with combination therapy of glyburide (or another sulfonylurea) plus metformin, if switched to GLUCOVANCE, the starting dose should not exceed the daily dose of glyburide (or equivalent dose of another sulfonylurea) and metformin already being taken. Patients should be monitored closely for signs and symptoms of hypoglycemia following such a switch and the dose of GLUCOVANCE should be titrated as described above to achieve adequate control of blood glucose.

Addition of Thiazolidinediones to GLUCOVANCE Therapy

For patients not adequately controlled on GLUCOVANCE, a thiazolidinedione can be added to GLUCOVANCE therapy. When a thiazolidinedione is added to GLUCOVANCE therapy, the current dose of GLUCOVANCE can be continued and the thiazolidinedione initiated at its recommended starting dose. For patients needing additional glycemic control, the dose of the thiazolidinedione can be increased based on its recommended titration schedule. The increased glycemic control attainable with GLUCOVANCE plus a thiazolidinedione may increase the potential for hypoglycemia at any time of day. In patients who develop hypoglycemia when receiving GLUCOVANCE and a thiazolidinedione, consideration should be given to reducing the dose of the glyburide component of GLUCOVANCE. As clinically warranted, adjustment of the dosages of the other components of the antidiabetic regimen should also be considered.

Specific Patient Populations

GLUCOVANCE is not recommended for use during pregnancy. The initial and maintenance dosing of GLUCOVANCE should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment requires a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of GLUCOVANCE to avoid the risk of hypoglycemia. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly. (See WARNINGS.)

HOW SUPPLIED

GLUCOVANCE® (Glyburide and Metformin HCl Tablets)

GLUCOVANCE **1.25 mg/250 mg** tablet is a pale yellow, capsule-shaped, bevel-edged, biconvex, film-coated tablet with **"BMS"** debossed on one side and **"6072"** debossed on the opposite side.

GLUCOVANCE **2.5 mg/500 mg** tablet is a pale orange, capsule-shaped, bevel-edged, biconvex, film-coated tablet with **"BMS"** debossed on one side and **"6073"** debossed on the opposite side.

GLUCOVANCE **5 mg/500 mg** tablet is a yellow, capsule-shaped, bevel-edged, biconvex, film-coated tablet with **"BMS"** debossed on one side and **"6074"** debossed on the opposite side.

GLUCOVANCE		NDC 0087-xxxx-xx for unit of use
Glyburide (mg)	Metformin hydrochloride (mg)	Bottle of 100
1.25	250	6072-11
2.5	500	6073-11
5	500	6074-11

STORAGE

Store at temperatures up to 25° C (77° F). [See USP Controlled Room Temperature.]

Dispense in light-resistant containers.

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PATIENT INFORMATION ABOUT
GLUCOVANCE® (Glyburide and Metformin HCl Tablets)

WARNING: A small number of people who have taken metformin hydrochloride have developed a serious condition called lactic acidosis. Properly functioning kidneys are needed to help prevent lactic acidosis. Most people with kidney problems should not take GLUCOVANCE. (See Question Nos. 9-13.)

Q1. Why do I need to take GLUCOVANCE?

Your doctor has prescribed GLUCOVANCE to treat your type 2 diabetes. This is also known as non-insulin-dependent diabetes mellitus.

Q2. What is type 2 diabetes?

People with diabetes are not able to make enough insulin and/or respond normally to the insulin their body does make. When this happens, sugar (glucose) builds up in the blood. This can lead to serious medical problems including kidney damage, amputations, and blindness. Diabetes is also closely linked to heart disease. The main goal of treating diabetes is to lower your blood sugar to a normal level.

Q3. Why is it important to control type 2 diabetes?

The main goal of treating diabetes is to lower your blood sugar to a normal level. Studies have shown that good control of blood sugar may prevent or delay complications such as heart disease, kidney disease, or blindness.

Q4. How is type 2 diabetes usually controlled?

High blood sugar can be lowered by diet and exercise, by a number of oral medications, and by insulin injections. Before taking GLUCOVANCE you should first try to control your diabetes by exercise and weight loss. Even if you are taking GLUCOVANCE, you should still exercise and follow the diet recommended for your diabetes.

Q5. Does GLUCOVANCE work differently from other glucose-control medications?

Yes it does. GLUCOVANCE combines two glucose-lowering drugs, glyburide and metformin. These two drugs work together to improve the different metabolic defects found in type 2 diabetes. Glyburide lowers blood sugar primarily by causing more of the body's own insulin to be released, and metformin lowers blood sugar, in part, by helping your body use your own insulin more effectively. Together, they are efficient in helping you achieve better glucose control.

Q6. What happens if my blood sugar is still too high?

When blood sugar cannot be lowered enough by GLUCOVANCE your doctor may prescribe injectable insulin or take other measures to control your diabetes.

Q7. Can GLUCOVANCE cause side effects?

GLUCOVANCE, like all blood sugar-lowering medications, can cause side effects in some patients. Most of these side effects are minor. However, there are also serious, but rare, side effects related to GLUCOVANCE (see Q9-Q13).

Q8. What are the most common side effects of GLUCOVANCE?

The most common side effects of GLUCOVANCE are normally minor ones such as diarrhea, nausea, and upset stomach. If these side effects occur, they usually occur during the first few weeks of therapy. Taking your GLUCOVANCE with meals can help reduce these side effects.

Less frequently, symptoms of hypoglycemia (low blood sugar), such as lightheadedness, dizziness, shakiness, or hunger may occur. The risk of hypoglycemic symptoms increases when meals are skipped, too much alcohol is consumed, or heavy exercise occurs without enough food. Following the advice of your doctor can help you to avoid these symptoms.

Q9. Are there any serious side effects that GLUCOVANCE can cause?

GLUCOVANCE rarely causes serious side effects. The most serious side effect that GLUCOVANCE can cause is called lactic acidosis.

Q10. What is lactic acidosis and can it happen to me?

Lactic acidosis is caused by a buildup of lactic acid in the blood. Lactic acidosis associated with metformin is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported in about one in 33,000 patients taking metformin over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the cases.

It's also important for your liver to be working normally when you take GLUCOVANCE. Your liver helps remove lactic acid from your bloodstream.

Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally.

There is no evidence that GLUCOVANCE causes harm to the kidneys or liver.

Q11. Are there other risk factors for lactic acidosis?

Your risk of developing lactic acidosis from taking GLUCOVANCE is very low as long as your kidneys and liver are healthy. However, some factors can increase your risk because they can affect kidney and liver function. You should discuss your risk with your physician.

You should not take GLUCOVANCE if:

- You have chronic kidney or liver problems
- You have congestive heart failure which is treated with medications, e.g., digoxin (Lanoxin®) or furosemide (Lasix®)
- You drink alcohol excessively (all the time or short-term "binge" drinking)
- You are seriously dehydrated (have lost a large amount of body fluids)
- You are going to have certain x-ray procedures with injectable contrast agents
- You are going to have surgery
- You develop a serious condition such as a heart attack, severe infection, or a stroke
- You are ≥80 years of age and have NOT had your kidney function tested

Q12. What are the symptoms of lactic acidosis?

Some of the symptoms include: feeling very weak, tired or uncomfortable; unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, or suddenly developing a slow or irregular heartbeat.

If you notice these symptoms, or if your medical condition has suddenly changed, stop taking GLUCOVANCE tablets and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.

Q13. What does my doctor need to know to decrease my risk of lactic acidosis?

Tell your doctor if you have an illness that results in severe vomiting, diarrhea, and/or fever, or if your intake of fluids is significantly reduced. These situations can lead to severe dehydration, and it may be necessary to stop taking GLUCOVANCE temporarily.

You should let your doctor know if you are going to have any surgery or specialized x-ray procedures that require injection of contrast agents. GLUCOVANCE therapy will need to be stopped temporarily in such instances.

Q14. Can I take GLUCOVANCE with other medications?

Remind your doctor that you are taking GLUCOVANCE when any new drug is prescribed or a change is made in how you take a drug already prescribed. GLUCOVANCE may interfere with the way some drugs work and some drugs may interfere with the action of GLUCOVANCE.

Q15. What if I become pregnant while taking GLUCOVANCE?

Tell your doctor if you plan to become pregnant or have become pregnant. As with other oral glucose-control medications, you should not take GLUCOVANCE during pregnancy.

Usually your doctor will prescribe insulin while you are pregnant. As with all medications, you and your doctor should discuss the use of GLUCOVANCE if you are nursing a child.

Q16. How do I take GLUCOVANCE?

Your doctor will tell you how many GLUCOVANCE tablets to take and how often. This should also be printed on the label of your prescription. You will probably be started on a low dose of GLUCOVANCE and your dosage will be increased gradually until your blood sugar is controlled.

Q17. Where can I get more information about GLUCOVANCE?

This leaflet is a summary of the most important information about GLUCOVANCE. If you have any questions or problems, you should talk to your doctor or other healthcare provider about type 2 diabetes as well as GLUCOVANCE and its side effects. There is also a leaflet (package insert) written for health professionals that your pharmacist can let you read.

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